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Natriuresis and Carbohydrate-Induced Antinatriuresis in Fasted, Hydrated Hypertensives (38798)

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An exaggerated natriuresis previously was observed to develop in some normal individuals fasted overnight and hydrated orally with water (1). The ingestion and, in some cases, infusion of glucose and/or insulin promptly eliminated this salt wasting. Numerous investigators (2–8) have demonstrated that acute volume expansion in hypertensive patients results in a more marked increase in urinary sodium excretion than is observed in otherwise comparable normotensive subjects. The one previous study on the effect of oral hydration with water in hypertensive patients failed to show any increase in urinary sodium excretion (9).

This series of studies in hypertensive subjects was undertaken to determine (1) if oral hydration produces a more frequent and/or more marked natriuresis in fasted hypertensive than normotensive subjects, and (2) if carbohydrate ingestion produces a more frequent and/or more marked antinatriuresis in hydrated hypertensive patients than in normotensive subjects. It also provided an opportunity to determine if glucose ingestion increased urinary calcium and magnesium excretions in hypertensives as it does in normotensive subjects. Finally, the effects of glucose ingestion on plasma concentrations and urinary excretions of zinc were evaluated.

Methods. Sixteen hypertensive volunteers, age 34–63 yr (mean age 49.8 yr), without cardiac decompensation or renal disease, were recruited from the ambulatory care programs of the Oklahoma City Veterans administration Hospital. The mean arterial pressures ranged from 112 to 159 mm Hg (mean ± SE 131 ± 3.4). The subjects were on unrestricted salt intakes (when hospitalized, a normal diet contains an estimated 7 g per day). The subjects were fasted after 6 PM and the next morning a urine sample was collected between 6 and 8 AM on an ad lib. water intake.

At 8 AM, each subject received an oral water load (20 cc H_2O/kg body weight). A prime of inulin and para-aminohippurate (PAH) was given followed by institution of a sustaining infusion of both agents in normal saline at a rate of 2 cc/min. An amount of water was given orally after each voiding so that the intravenous and oral fluid intake matched urine output. Subjects remained recumbent throughout the study except for short periods when allowed to stand for spontaneous voluntary voiding.

After a near maximum diuresis was established and a 30- to 40-min equilibration period allowed for the clearance studies, urine samples were collected for three 20-min periods and blood samples were collected at the midpoints of the first and third periods.

Glucose (1.5 gm/kg body weight) in 200 ml water then was ingested and urines were collected for an additional four 20-min periods. Bloods were drawn at the midpoints of the 2nd and 4th postglucose ingestion periods, i.e., 30 and 70 min after glucose ingestion. The mean of the first three periods was used to calculate the preglucose urinary excretions; the mean of the 5th through 7th periods was used to calculate the postglucose urinary excretions. In four additional hypertensive subjects on an ad lib. water intake (control group A), urinary sodium and potassium excretions were quantified on 2-hr urine samples collected between 6 and 8 AM and between 8 and 10 AM.

Another seven hypertensive subjects (control group B), were studied without hydration but were given the standard inulin and PAH priming loads and sustaining infusions at 8 AM. Three 20-min urine samples were collected after a 30-min equilibration period.

Determinations were made on urine and plasma samples for sodium, potassium, inulin, and PAH using methods previously described (10). Serum and urine calcium, magnesium and zinc concentrations were determined with the Perkin-Elmer 303 atomic absorption spectrophotometer (11). Osmolalities were determined using a Fiske osmometer.

In six hydrated subjects, ^{131}I-labeled albumin (RISA) was injected (5 μCi) along with the inulin and PAH prime. Plasma samples were drawn 15 min after injection to obtain a baseline plasma volume (100% of injected RISA). Further plasma samples were collected at the midpoints of 1st, 3rd, 5th, and 7th urine collection periods and the concentrations (counts per minute) were compared against the baseline value. Student's t tests for paired and unpaired data were used for statistical analysis.

Results. In 11 hypertensive patients fasted overnight, oral hydration (20 cc H_2O/kg body weight) significantly increased ($P < 0.01$) urinary sodium and potassium excretions. The mean ± SE sodium excretions increased from 130 ± 16 (6–8 AM) to 291 ± 28 μeq/min (8–10 AM); the mean potassium excretions increased from 42 ± 6 to 96 ± 10 μeq/min. To insure that these increases were not due to diurnal variations in sodium excretion, urine samples were collected between 6 and 8 AM and between 8 and 10 AM in four hypertensive subjects fasted overnight and allowed ad lib. hydration. Mean urinary sodium excretions were 90 ± 20 μeq/min between 6 and 8 AM and 101 ± 17 μeq/min between 8 and 10 AM. To insure that the solute load created by the priming loads and sustaining infusions of inulin and PAH in saline would not explain the natriuresis observed after hydration, seven hypertensive subjects were studied without hydration before and after inulin and PAH administration. Mean urinary sodium excretions increased from 111 ± 22 to 193 ± 32 μeq/min. This increase in sodium excretion was not statistically significant. Furthermore, when one compares the increase in sodium excretion in the hydrated hypertensives with the nonhydrated hypertensives receiving inulin and PAH, there is a statistically significant increase ($P < 0.05$) in the former group.

Previous studies (1) showed that after an overnight fast and oral hydration with tap water, some subjects developed a natriuresis (6 of 22 subjects, or 27%, excreted more

TABLE I. URINARY SODIUM AND POTASSIUM EXCRETIONS AND INULIN CLEARANCES (MEAN ± SEM) IN 11 HYPERTENSIVE SUBJECTS BEFORE AND AFTER HYDRATION WITH 20 CC H_2O/KG BODY WEIGHT AT 8 AM.[a]

	Pretreatment values 6–8 AM	Posttreatment values 8–10 AM
Hydrated hypertensives		
Sodium excretion (μeq/min)	130±16	291±28*
Potassium excretion (μeq/min)	42±6	96±10*
Inulin clearance (cc/min)		110±5.9
Control group A		
Sodium excretion (μeq/min)	90±20	101±17
Potassium excretion (μeq/min)	41±7	36±4
Control group B		
Sodium excretion (μeq/min)	111±22	193±32
Potassium excretion (μeq/min)	40±8	52±11
Inulin clearance (cc/min)		115±8.6

[a] A loading dose of inulin and PAH also was given and constant infusion started at 8 AM. Three urine collections were obtained 30 min after the prime at 20-min intervals. Four additional hypertensive subjects (control group A) were studied without hydration or inulin–PAH loads to evaluate changes which might be related to diurnal rhythm. Another seven hypertensive subjects were studied without hydration but with standard inulin–PAH infusions to distinguish the effect of the osmotic loads of these agents from the effects of the hydration.

* Posttreatment values significantly greater than pretreatment values ($P < 0.01$). Increase in posttreatment values in hydrated subjects significantly greater than increases in posttreatment values observed in control group B ($P < 0.05$).

than 200 μeq of sodium per minute). Nine of 22 (41%), including five of the six patients with an initial natriuresis, developed more than a 30% decrease in urinary sodium excretion after an oral glucose load (100 g). In present study in 16 hypertensive patients, 12 (75%) developed a comparable natriuresis. Ten subjects (62%) had more than a 30% decrease in urinary sodium excretion (Table I and Fig. 1). No correlation appeared to exist between the magnitude of the natriuresis or carbohydrate-induced antinatriuresis and the mean arterial blood pressure however. Although no control studies were conducted in this hypertensive population omitting only the glucose ingestion, a number of control studies in our previous report (1) showed that sodium excretion did not decrease acutely as it did after glucose ingestion.

In six patients allowed to develop a maximum diuresis after hydration (Table II), the ingestion of glucose caused a fall in urine volume, mean urinary sodium excretion, and osmolal clearance (C_{osm}). Free water clearance (C_{H_2O}), in contrast, remained constant suggesting the enhanced sodium reabsorption observed after glucose ingestion occurs principally in the proximal tubule and/or diluting segment of the distal tubule.

In six patients, ^{131}I-labeled albumin (RISA) was injected intravenously along with inulin and PAH in order to document any shifts in plasma volume which might explain the antinatriuresis after carbohydrate ingestion. The disappearance curve of the ^{131}I-labeled albumin before and after carbohydrate ingestion continued along a straight line (log scale) suggesting that no fluid shift occurred (Fig. 2). If water had moved intracellularly due to a shift of solute (glucose, potassium, phosphorus, etc.) intracellularly after glucose ingestion, an increase in the concentration of ^{131}I-labeled albumin in the plasma should have been observed.

Plasma concentrations and urinary excretions of potassium, calcium, and magnesium also were followed to compare the response to a carbohydrate load in these hypertensive subjects vs that observed in previously studied normotensive subjects (Table II). Mean urinary calcium and magnesium excretions failed to increase as much in this hypertensive group as thep did in previously studied normal subjects. Plasma calcium and magnesium excretions remained unchanged. The decrease in plasma concentrations and urinary excretions of potassium were of similar magnitude in the two groups.

Serum zinc concentrations fell significantly ($P < 0.01$) from a mean ± SEM of 84 ± 4 μg/100 ml prior to glucose in-

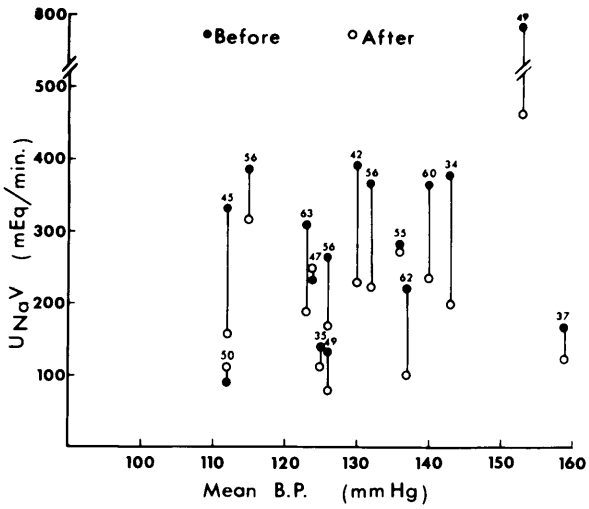

FIG. 1. Urinary sodium excretions (μeq/min) in 16 hypertensive subjects before and after glucose ingestion plotted against their mean arterial blood pressures. The subject's age is inscribed above the data.

TABLE II. MEAN (± SEM) URINARY EXCRETIONS AND PLASMA CONCENTRATIONS OF SODIUM AND POTASSIUM, AND INULIN CLEARANCES IN 16 HYPERTENSIVE SUBJECTS 1–2 HOURS AFTER HYDRATION (0–60 MIN) AND AFTER INGESTION OF 1.5 G OF GLUCOSE PER KG BODY WEIGHT (80–140 MINUTES). IN SIX SUBJECTS, URINARY EXCRETIONS AND PLASMA CONCENTRATIONS OF CALCIUM, MAGNESIUM, AND ZINC, AND OSMOLAL AND FREE WATER CLEARANCES ALSO WERE STUDIED.

	Urine μeq/min	Plasma meq/liter	Clearance cc/min	Urine μeq/min	Plasma meq/liter	Clearance cc/min
16 Subjects						
Urine flow			11.8±1.3			10.5±1.3
Sodium	303±41	136±0.7		201±24**	136±0.8	
Potassium	91±8	4.0±0.1		52±5**	3.8±0.1*	
Inulin clearance			110±6			112±5
Six subjects						
Sodium	287±38	137±0.3		201±29**	137±0.6	
Potassium	102±9	4.0±0.1		56±8**	3.9±0.2	
Calcium	8.3±1.7	4.4±.04		11.2±2.1**	4.2±.16	
Magnesium	4.5±1.2	1.4±.04		7.2±1.9**	1.4±.06	
Zinc	0.7±.16	84±4		0.8±.17	72±4**	
	(μg/min)	(mg/100 cc)		(μg/min)	(mg/100 cc)	
Osmolal clearance			4.0±0.3			3.5±0.3
Free water clearance			10.9±1.1			11.1±1.0

* $P < 0.05$; ** $P < 0.01$.

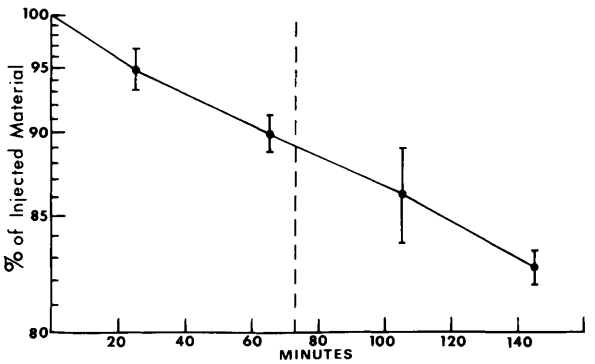

FIG. 2. The plasma disappearance curve (mean ± SEM) of ^{131}I-labeled albumin in six hypertensive subjects plotted on a log scale. The zero point in time is 15 min after administration of the isotope and is considered 100%. The dashed line represents the point when glucose was ingested.

gestion to 72 ± 4 μg/100 ml after glucose ingestion. Urinary zinc excretions were not altered by the ingestion of glucose.

Discussion. Patients with essential hypertension have an exaggerated natriuresis after the rapid intravenous infusion of sodium chloride, glucose, or mannitol solutions when compared to normotensive subjects (2–8). This augmented response has been attributed to an increased glomerular filtration rate (2), to a decrease in tubular sodium reabsorption in the proximal tubule (2, 4) and distal nephron (loop of Henle) (3), to a redistribution of blood flow from corticomedullary to cortical (salt-losing) nephrons (5), and to an increase in a humoral natriuretic substance (12). Buckalew *et al.* (3), in a recent critical discussion, felt that the exaggerated natriuresis in their hypertensive patients, based on an analysis of free water clearances, could be explained by a defect in distal (loop of Henle) sodium transport. They acknowledge that a proximal tubular effect cannot be excluded. The

intrarenal mechanisms remain to be precisely defined.

Schalekamp *et al.* (8) found that an accentuated natriuresis consistently occurred in older hypertensive patients in whom renal vascular resistance and filtration fraction were elevated and plasma renin was suppressed. Krakoff (6) found that a group of hypertensives failing to increase renin levels in response to acute volume reduction with diuretics ("renin-unresponsive") developed a more marked natriuresis than did an otherwise comparable "renin-responsive" group.

Conflicting results are reported in the literature on whether oral hydration with water alone can result in sufficient extracellular fluid volume expansion to increase urinary salt excretion in hypertensive or normotensive subjects (9, 13, 14). Well-controlled studies by one group (9, 14) failed to demonstrate an increase in urinary sodium excretions with oral hydration in either normotensive or hypertensive subjects. Other studies (13), in agreement with our previous (1) and present experiences, showed a significant natriuresis with hydration. Two possible explanations for these discrepancies can be found. In the first studies (9, 14) all subjects were under 31 yr whereas in our two studies, the mean ages were 56 and 50 yr. As observed by Schalekamp *et al.* (15), older subjects appeared to respond to hydration with a greater natriuresis. Secondly, in our studies (1) and in those of Kruck and Kreuke (13), the patients were fasted at least 12 hr prior to study; in the first studies (9, 14) it is only reported that breakfast was withheld. Ingestion of carbohydrate prior to the study might have prevented development of a natriuresis after hydration. One potential explanation for the antinatriuresis observed after carbohydrate ingestion is that the hyperglycemia increases circulating insulin levels and shifts glucose, potassium, phosphate, and other osmotically active substances intracellularly. This intracellular shift of solute along with osmotically obligated water would cause a decrease in extracellular fluid and plasma volumes and explain the decreased urinary sodium excretions. The more frequent carbohydrate-induced antinatriuresis observed in hypertensive patients compared to normotensive subjects might be due to such a shift of solutes and fluids superimposed upon an already decreased plasma volume seen in hypertensives. Serial ^{131}I-labeled albumin concentrations followed in six patients failed to show any evidence of an increase in isotope concentration indicative of a shift of fluid (and solute) intracellularly after glucose ingestion. The fall in urine volume, urinary sodium excretion, and osmolal clearance with no change in free water clearance after glucose ingestion is consistent with an enhanced sodium reabsorption in the proximal tubule and/or diluting segment of distal tubule. Suki *et al.* (15) recently presented evidence that a glucose load sufficient to exceed slightly the renal threshold for glucose absorption enhanced bicarbonate reabsorption in bicarbonate-loaded dogs. This enhanced bicarbonate reabsorption, presumably in the proximal tubule, could be blocked by phlorizin, an agent which also blocks glucose absorption. Whether the enhanced bicarbonate reabsorption was responsible for or secondary to the increased sodium reabsorption remains unclear but the authors discussed evidence suggesting that the enhanced bicarbonate reabsorption might be the primary event. The possibility remains that the antinatriuretic effect of glucose ingestion might be related to a direct effect on renal metabolism, such as a limitation of some substrate(s) necessary for the energy used to facilitate sodium reabsorption during fasting, or by an interaction of carbohydrate metabolism with the production or action of some humoral salt-active substance.

In normal young subjects, ingestion of an oral carbohydrate load has little effect on urinary sodium excretion but increases urinary calcium and magnesium excretions 2- to 3-fold (10). The increases in urinary calcium and magnesium excretion in the hypertensive patients after glucose ingestion were less than 2-fold. This difference between the hypertensive patients and normal young subjects is best explained by an enhanced reabsorption of sodium in the proximal tubule paralleled by calcium and mag-

nesium reabsorption at that site. These findings in our hypertensive population are similar to those described in healthy young men with chronic extracellular volume expansion induced by chronic deoxycorticosterone acetate (DOCA) administration before and after glucose ingestion (16).

Davies *et al.* (17) reported that plasma zinc levels decreased 12% after ingestion of 50 g of glucose. McBean and Halsted (18) failed to confirm this observation finding no change in plasma zinc concentrations after ingestion of a test breakfast containing not only carbohydrate but protein and fat. The falls in plasma zinc concentrations observed in Davies *et al.*'s and our studies are not due to an increases in urinary zinc excretions but apparently represent an intracellular shift of this trace metal paralleling the shifts in potassium and phosphate after glucose ingestion. In contrast, plasma calcium and magnesium concentrations remained constant.

Summary. After an overnight fast and oral hydration with water, hypertensive subjects developed a significant natriuresis (mean urine sodium excretions increased from 130 to 291 μeq/min). The incidence of a natriuresis (>200 μeq sodium excreted per minute) was 75% in the hypertensive group (16 subjects) compared to 27% in a previously studied normotensive group (22 subjects). The incidence of a carbohydrate-induced antinatriuresis (>30% decrease in urinary sodium excretion) was 62% in the hypertensive group compared to 41% in the normotensive group. No decrease in plasma volume (^{131}I-labeled albumin concentration) due to a shift of solute and water intracellularly could be documented to explain the antinatriuretic effect of glucose. An incidental observation was a significant decrease in plasma zinc concentrations after glucose ingestion.

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